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Bronchial valve treatment for pulmonary air leak after anatomic lung resection for cancer.

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Take home message: Bronchial valve placement is an effective and safe treatment for a pulmonary air leak after lung resection.

Key words : bronchial valve treatment - digital drainage system - lung cancer - surgery

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Abstract.

A persistent postoperative pulmonary expiratory air leak after an anatomic pulmonary resection is usually managed conservatively, but can be associated with significant morbidity and increased costs. The use of bronchial valves is a minimally invasive method that may be an effective and safe treatment in this setting.

In a prospective study, the clinical efficacy of intrabronchial valve treatment in patients with a prolonged persistent pulmonary air leak after anatomic surgical resection for cancer was investigated.

Ten out 277 patients with anatomical pulmonary resection for cancer were included, and 90% were scheduled for valve treatment. We demonstrated an air leak cessation at a median of 2 days after valve placement, which resulted in a chest tube removal at a median of 4 days after valve placement. Elective removal of the intrabronchial valves could be safely planned 3 weeks after valve implantation. Lung function alteration associated with airway occlusion by valves was limited.

Intrabronchial valve treatment with the aid of a digital thoracic drainage system is an effective and safe therapy for patients with a prolonged pulmonary air leak after anatomic lung resection for cancer.

Introduction.

About 50,000 patients are potential candidates each year for a surgical resection for early stage lung cancer in the U.S.[1] A prolonged pulmonary air leak in this setting is independently associated with prolonged hospital length of stay, decreased patient satisfaction, increased morbidity or postoperative complications, and adds significantly to the health care cost.[2,3] The use of bronchial valves was first considered a potential effective salvage procedure for the treatment of a persistent pulmonary air leak in patient who were no suitable candidates for any other surgical treatment.[4,5] Retrospective case series provided scientific evidence that removable bronchial valves are a safe and effective intervention for alveolar-pleural fistula with persistent pulmonary air leak.[6,7] Limitations of reported case studies and series are their retrospective nature, chest tube monitoring mainly based on a subjective assessment of the air leak reduction, and heterogeneity of disorders causing the persistent air leak. We therefore decided to perform a prospective study objectively evaluating the efficacy and safety of airway closure using intrabronchial valves for the treatment of a persistent postoperative air leak after an anatomic lung resection for cancer. For this purpose, we assessed air leak monitoring during and after intrabronchial valve treatment using a digital thoracic drainage system, and respiratory function alteration linked to temporary airway closure.

Methods.

This is a prospective, observational, single center study (clinicaltrials.gov identifier NCT01451359), evaluating the efficacy of intrabronchial valve treatment in consecutive patients with a prolonged persistent pulmonary air leak after anatomic surgical resection for cancer.

Patients.

Inclusion criteria were prolonged (10±3 days postoperative) persistent air leak refractory to conventional treatment (such as prolonged drainage and/or perioperative chemical pleurodesis), anatomical lung resection (such as segmentectomy, (bi)lobectomy or sleeve lobectomy), air leak after antero/posterolateral thoracotomy or video-assisted thoracoscopy (VATS), and expiratory air leak of any size which is at least 100mL/min measured by a digital thoracic drainage system (Thopaz, Medela AG). Patients were excluded whenever the postoperative prolonged air leak was present for more than 13 days, a pneumonectomy or non-anatomical lung resection was performed, a lung resection for another indication than

cancer was performed, a previous Heimlich valve was applied, in case of empyema, or whenever the patient was unable to give an informed consent. A thoracic surgeon assessed the patients during their early postoperative period. A 'diagnostic balloon occlusion test' by flexible bronchoscopy under local anesthesia was required in order to assess whether the air leak could be stopped and/or whether the patient could tolerate the provocative (sub)lobar occlusion. All patients provided written informed consent after study approval by a Local Institutional Review Board (B32220096119).

Study procedures.

The chest tube was connected to a digital thoracic drainage system (Thopaz, Medela AG, Switzerland) continuously measuring and displaying the air leak, while the suction level was standardized at -8cmH20 in all patients. During the scheduled 'diagnostic balloon occlusion test' by flexible bronchoscopy under local anesthesia with moderate sedation, a balloon catheter is passed through the working channel of the bronchoscope, placed in the suspected segmental bronchi and inflated until complete occlusion of segmental bronchi. A sequential balloon occlusion of segmental or lobar airways was performed with the aim to truly stop the air leak (defined as air leak <20ml/min^{-1} as displayed on the Thopaz system) and thus attribute the air leak to the particular segment tested, but also to test whether the patient could clinically tolerate a (sub)lobar occlusion similar as after intrabronchial valve treatment. Only patients with an identified target lobe/segment for valve treatment and tolerable airway occlusion were considered for subsequent intrabronchial valve treatment.

Intrabronchial valve treatment was performed using the Spiration Inc. (d/b/a Olympus Respiratory America) intrabronchial valve and delivery catheter (IBV^{TM} Valve System), according to a predefined protocol of IBV sizing and placement. The valve treatment was scheduled on the same day or the day after the 'diagnostic balloon occlusion test' bronchoscopy. The procedure was performed under general anesthesia with an 8Fr endotracheal tube applying inspiratory positive pressure mechanical ventilation (standardized IPPV settings: TV 8ml/kg - frequency 12x/' - FiO2 50% - no PEEP). The first step of valve placement is the airway sizing using the IBV airway sizing kit, to determine the appropriate valve size (5, 6, or 7 mm). Once the appropriate valve is loaded into an IBV catheter, the catheter is advanced through the working channel of the bronchoscope into the target airway segment where valve deployment is performed. A continuous digital air leak assessment before and during valve placement enables a logical and stepwise occlusion of (sub)segmental

bronchi until air leak cessation is obtained during digital air leak monitoring. The complete description of the procedure is reported elsewhere.[8] The patient is extubated in the endoscopy suite once the last valve is inserted. In the recovery room, the air leak is digitally assessed during spontaneous breathing and a chest X-ray is made to assess the lung inflation status. The Thopaz system is kept at -8cmH20 suctioning and air leak flow is continuously measured enabling the treating physician to decide upon chest tube removal once the air leak is stopped for at least 8 hours.

All patients were scheduled to have a chest X-ray and pulmonary function test 3-4 weeks after endoscopic valve placement. After these measurements, a preplanned removal of all intrabronchial valves was scheduled between day 21 and 28 after valve placement, and performed during a flexible bronchoscopy under local anesthesia with moderate sedation. Within 7 days after removal of the valves, a control chest X-ray and pulmonary function test were performed.

Outcome measures.

The primary study endpoint is the clinical efficacy on air leak cessation allowing chest tube removal. Other evaluations included: avoidance of Heimlich valve, avoidance of additional surgical intervention and safety issues including complications related to intrabronchial valve treatment (e.g. pulmonary infection, valve migration, pneumothorax requiring treatment, respiratory insufficiency) and evaluation of consequences of airway closure on pulmonary function, the direct cost related to the device used, and finally, timing of bronchial valve removal.

Statistics.

Data analysis was performed with a statistical software package, GraphPad Prism 4 for Windows (San Diego, CA, USA). Differences within each group at different time points were tested using a paired *t*-test. A p-value <0.05 was considered as significant.

Results.

Study population, clinical and procedural characteristics (**Table 1 and 2**).

Between October 2011 and April 2013, 277 patients underwent a lobectomy, bilobectomy or segmentectomy for cancer in a single institution, of whom 65% by VATS and 35% by open thoracotomy. A persistent air leak eligible for the study occurred in 12 (4.3%) patients.

Two patients were eligible but were not included as they declined study participation. Ten patients with evidence of an air leak >100ml/min at postoperative day 10±3 were included and evaluated for air leak closure during a 'diagnostic balloon occlusion test' bronchoscopy. Demographic characteristics of all patients that entered the study are presented in **Table 1**. Procedure related characteristics on the day of IBV treatment are listed in **Table 2**. The median duration of postoperative air leak before valve treatment was 7 days (range 7-13), the median air leakage was 490 ml/min, and a median amount of 4 IBV valves were implanted. One patient (patient N° 4) was not scheduled for intrabronchial valve treatment under general anesthesia. He had a calculated ppoFEV1 of 37% and ppoDLco of 46% for right sided bilobectomy superior, and experienced suffocation during the 'diagnostic balloon occlusion test' of the remaining lower lobe bronchus while a selective more distal occlusion didn't result in air leak cessation. In addition his preoperative perfusion scan demonstrated a 67% perfusion to the right lung. Thus, in ITT, 90% of the patients were scheduled for intrabronchial valve treatment.

Outcome measures (**Table 3-5**).

The primary study outcome measurement demonstrated a median air leak cessation at 2 days after valve treatment, which resulted in chest tube removal in the patients receiving valves at a median of 4 days (range 1-14 days) after valve placement (**Table 3**).

On day +1 after valve placement, the air leak was reduced by 90-100% in six patients, while in three patients a reduced air leak recurrence (defined as <50% of its initial value) was observed despite the fact that nearly complete air leak cessation had been demonstrated at valve implantation under general anesthesia (**Table 4**). In these patients a minimal intrabronchial valve displacement (without migration) was documented during flexible bronchoscopy under local anesthesia. Shallow depth of the target bronchus was judged to be the main reason for these displacements: the anchor points were positioned in a more distal bronchus, resulting in suboptimal axis of the valves and inadequate fitting of the valve umbrella in the targeted bronchus. These patients were discharged (two on day 3 and one on day 7 after valve treatment) with a Heimlich valve connected to their chest tube. In these three patients the chest drain could be removed at day 14 after intrabronchial valve treatment, and an additional surgical intervention was not required.

During the entire study, no deaths, no cardiovascular complications, or no implant-related events such as infection distal to the intrabronchial valve, lobar atelectasis, hemoptysis,

persistent cough, pneumothorax or expectoration of a valve did occur. One patient (patient N° 10) suffered from respiratory insufficiency requiring NPPV during 2 weeks until valve removal. This patient had a calculated ppoFEV1 of 35% and developed a massive prolonged air leak with subcutaneous emphysema after an upper lobe lobectomy, requiring intrabronchial valve treatment of almost the entire lower lobe.

All patients underwent spirometry a few hours before valve removal and a follow-up spirometry within a week after valve removal allowing calculation of the magnitude of lung function alteration associated with valve occlusion (**Table 5**). A significant decrease in FEV1 was found at airway closure by valve implantation (mean FEV1 53% versus 61% predicted; p=0.0002). A 5-10% decrease in FEV1 predicted was observed in patients when a right upper lobe was treated with intrabronchial valves, while a 10-15% decrease in FEV1 predicted was observed when a lower lobe was treated with intrabronchial valves. The removal of the intrabronchial valves was performed at a median of 23 days (range 14-28 days) (**Table 3**). In one patient (patient N° 10) valve removal was performed earlier, at day 14 as valve treatment induced respiratory insufficiency. No single patient developed a pneumothorax after elective valve removal. Recurrence of air leak associated with valve displacement in three patients was not associated with delayed valve removal beyond the pre-planned period.

The cost of one IntraBronchial Valve is 1500 €, while the cost of instruments for placement is 970 € (600 € for the deployment catheter and loader, 200 € for the IBV airway sizing kit, and 170 € for the balloon catheter). The median direct cost related to valve management was 6,970 € (range 2,470-14,470) per patient.

Discussion.

This is the first prospective study to evaluate the efficacy of intrabronchial valve treatment for a prolonged pulmonary air leak in a well-defined patient group after anatomic lung resections for cancer using accurate measurements of the expiratory pulmonary air leak. The treatment approach and algorithm based on quantitative air leak monitoring lead to successful air leak cessation at a median of 2 days after valve therapy and chest tube removal at a median of 4 days after valve therapy. Overall, a Heimlich valve could be avoided in 6 out of 10 patients. Moreover we could prove a safe valve removal 3 weeks after valve therapy. This interval is feasible as a visceral pleural tear will be epithelialized after 3 weeks.

A postoperative pulmonary air leak after an anatomic pulmonary resection is usually managed conservatively, such as a longer period of chest tube drainage or the use of a Heimlich valve. But it must be stressed that also different other strategies have been used and no unique algorithm has been validated.[9] There is no standard definition for a persistent pulmonary air leak in the literature, but an air leak has been considered a complication only when it persists beyond the normal hospital stay. A median hospital stay after a lobectomy is 4-7 days, and therefore a prolonged persistent pulmonary air leak could be defined as one that is still present on postoperative day 7. Data from the ESTS 2012 database show that the percentage of air leak present on day 5 is 8.3% for lobectomy, 6.8% for segmentectomy and 11.1% for bilobectomy.[10] Apart from a prolonged hospital length of stay and increased morbidity or postoperative complications, a persistent postoperative pulmonary air leak may also impede the opportunity of adjuvant chemotherapy in cases where this is indicated.

Our study conclusions support the earlier retrospective series suggesting that bronchial valve therapy using the IBV^{TM} Valve system for prolonged air leak has an acceptable safety and efficacy for the treatment of a prolonged pulmonary air leak.[6,7] Accordingly, the U.S. Food and Drug Administration approved in 2008 the IBV^{TM} Valve System for use in the treatment of prolonged air leaks of the lung, or significant air leaks that are likely to become prolonged air leaks following lobectomy, segmentectomy, or lung volume reduction surgery.[11] There are, however, several clinical differences which can be appreciated compared to prior series (**Table 6**). We decided to restrict the indication for valve treatment to patients with persistent air leak after an anatomic pulmonary resection (as suggested by FDA approval), and thus not include patients who had an air leak caused by a spontaneous pneumothorax or a pleural decortication procedure (e.g. for empyema or mesothelioma). This choice might explain the fact that a higher candidature rate for valve treatment was observed (90% versus 80%) and a higher rate of successful chest tube removal was observed (100% versus 63-75%). Our patients might have had a 'more localized' pleural injury and/or better pulmonary function and thus respiratory reserve, as they were previously considered medically fit to undergo a pulmonary resection. We were also able to further reduce the time until chest tube removal from a median of 1-2 weeks towards a median of 4 days. This can be explained by the use of a digital thoracic drainage system which enables continuous monitoring of the air leak not only helpful for appropriate valve placement but also for more precise timing of chest drain removal.[12-14] Finally, previous reports reevaluated patients approximately 6 weeks after valve placement to determine whether the valve removal is a

feasible option. We clearly demonstrated an uneventful valve removal 3 weeks after valve placement in all patients.

The decreased FEV1 suggest that respiratory compromise associated with airway closure may be a potential side effect of air leak treatment with intrabronchial valves, in particular when this leak complicates lobectomy. This drawback seems limited as the initial 'diagnostic balloon occlusion test' may allow excluding the more disabled patients and limiting the number of respiratory failures. In addition, valve treatment is an easily reversible procedure offering a quick answer in case of significant post-treatment respiratory insufficiency, just as in our case N° 10 in who we decided to remove the valves after 14 days which we considered enough for pleural reepithelialisation. Finally, no atelectasis was observed after valve implantation and no other valve related complication was observed. Altogether, these observations allow us to conclude that this procedure is safe.

This study has the following potential limitations. This was a prospective non-randomized study. Thus the true benefit compared to any other standard approach (e.g. watchful waiting, ambulatory Heimlich valve, or surgical intervention) or a cost-effectivenes analysis have not been assessed yet. In addition, a true quantitative criterium (duration and quantity) for a prolonged air leak requiring further intervention does not exist. Our inclusion criteria seem acceptable since patients with failure of valve treatment (i.e. finally requiring a Heimlich valve) were in fact those with the smallest prolonged air leak. Furthermore, while the valve treatment was performed under general anesthesia with positive pressure ventilation, we observed the day after the procedure a slight valve displacement in 3 patients. This valve displacement caused a recurrence of the air leak to a lesser extent than was the case before valve placement (≥50% reduction), resulting in a short period of ambulatory Heimlich valve treatment. Finally, the number of patients seems limited but is must be stressed that a prolonged air leak fortunately remains an uncommon complication (4.3% in our cohort of anatomic pulmonary resections for cancer) and we believe that a larger number of patients wouldn't significantly change our results.

In conclusion, the application of a digital thoracic drainage assessment of the pulmonary air leak might guide intrabronchial valve placement and allow a safe fast-tracking chest tube removal in patients with a persistent air leak after a pulmonary resection for cancer. Air leak closure can be obtained with minimal airflow alteration by intrabronchial valves leading to chest tube removal in all patients.

Tables.

Table 1. Demographic data of patients that entered the study.

Characteristics of patients evaluated	**Outcome**
Gender, M/F	9/1
Age, median (range)	67 (46-75)
Anatomical resection, lung cancer/metastasis	9/1
COPD (Tiff <0.70), %	70%
median FEV1, % predicted (range)	79% (41-97)
median ppoFEV1, % predicted (range)	66% (35-87)
median DLco, % predicted (range)	71% (58-80)
median ppoDLco, % predicted (range)	60% (43-67)

M, male ; F, female ; COPD, chronic obstructive pulmonary disease ; Tiff, Tiffeneau index.

Table 2. Characteristics at intrabronchial valve placement.

		Duration of air leak, days	Volume of air leak, ml	Pleural space, mm	SubQ Em.	Segments treated (IBV)	Number of valves
1	VATS lobectomy RLL	7	2000	0	y	RB 1-2-3	4
2	VATS lobectomy RLL	7	1200	0	y	RB 1-2-3	4
3	VATS lobectomy RUL	7	500	30	y	RB 6	1
4	Thoracotomy RUL+RML	9	200	20	y	na	na
5	VATS segmentectomy apex RUL	13	360	31	n	RB 2-3	2
6	VATS lobectomy RUL	13	180	55	y	RB 6	4
7	VATS lobectomy RUL	7	180	60	y	RB 6-7-8-9-10	5
8	Thoracotomy LUL	7	720	0	y	LB 8-9-10	9
9	Thoracotomy LUL	8	2500	20	y	LB 6-9-10	6
10	VATS lobectomy RUL	7	480	20	y	RB 6-8-9-10	7
	Median	**7**	**490**	**20**	**-**	**-**	**4**

ml, milliliter ; VATS, video-assisted thoracic surgery ; Pleural space, measured on chest X-ray as distance between cupola and apex of the lung ; SubQ E, subcutaneous emphysema (assessed on chest X-ray) ; y, yes ; n, no ; IBV, intrabronchial valve ; RLL, Right lower lobe ; RUL, right upper lobe ; RB, right segmental bronchus ; LB, left segmental bronchus ; na, not applicable.

Table 3. Characteristics during follow-up.

Patient N°.	Airleak, days	Chest tube, days	IBV, days
1	2,0	4	21
2	3,5	5	28
3	0,5	3	21
5	0,0	1	24
6	3,0*	14	27
7	3,0*	14	23
8	7,0*	14	28
9	0,0	4	18
10	0,0	4	14
Median	**2,0**	**4**	**23**

* patients 6, 7 and 8 : documented dislocation of one endobronchial valve was responsible for recurrence of a reduced air leak; these patients were discharged with a Heimlich valve.

N°, number ; IBV, intrabronchial valve

Table 4. Quantitative evolution of the air leak from day -1 till day +4 (d+0 = day of IBV placement).

Patient N°.	Air leak d-1, ml	Air leak d+0, ml	Air leak d+1, ml	Air leak d+4, ml
1	2000	100	130	0
2	1200	20	100	0
3	500	20	0	0
5	360	0	0	0
6	180	30	90	30*
7	180	10	80	50*
8	720	30	200	50
9	2500	0	0	0
10	480	0	0	0

* patients 6 and 7 were discharged with a Heimlich valve on day +3.

IBV, intrabronchial valve ; ml, milliliter ; d, day.

Table 5. Functional consequences of intrabronchial valve removal.

Patient N°	Target lobe	FEV1, % pred (1)	FEV1, % pred (2)	Δ *FEV1, %*
1	RUL	56	67	**11**
2	RUL	71	78	**7**
3	apex RLL	60	61	**1**
5	RUL	48	53	**5**
6	apex RLL	67	75	**8**
7	RLL	47	60	**13**
8	LLL	56	70	**14**
9	LLL	49	58	**9**
10	RLL	19	28	**9**

N°, number ; FEV1, Forced Expiratory Volume in 1 second ; pred, predicted value ; (1), spirometry performed before valve removal (on the day of valve removal, before the procedure) ; (2), spirometry performed within a week after valve removal ; RUL, right upper lobe ; RLL, right lower lobe ; LLL, left lower lobe.

Table 6. Comparison of published studies on bronchial valve treatment for persistent pulmonary air leak.

Author	**Gillespie et al.**	**Firlinger et al.**	**Current study**
Study design and aim	**Retrospective Safety & efficacy**	**Retrospective Efficacy**	**Prospective Efficacy**
Air leak assessment	Visual (bubbles)	Digital (Thopaz)	Digital (Thopaz)
Reason prior chest intervention	Pleura + Lung	Pleura + Lung	Lung
Median chest tube / air leak duration before valve treatment	28 days	17 days	7 days
Candidate for valve treatment	78%	81%	90%
Median number of valves used	3.5	1	4
Successful chest tube removal	75%	63%	100%
Median time to chest tube removal	16 days (10-36)	8 days (1-21)	4 days (1-14)
Mean time to valve removal	37 days (14-55)	NR	23 days (14-28)

NR, not reported.

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